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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,038	08/18/2003	C. Frank Bennett	ISPH-0764	3074

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ISIS PHARMACEUTICALS INC
1896 RUTHERFORD RD.
CARLSBAD, CA 92008

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/643,038	BENNETT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-18-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 3-4-04.

Claims 1, 2, 4-10, 12-15 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-10, 12-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to compositions and methods of inhibiting the expression of human phospholipase A2, group IIA comprising the administration of compounds between 8-50 nucleobases which specifically hybridize with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA. The specification and claims do not adequately describe the distinguishing features or attributes concisely shared by the members of the claimed genus comprising a compound between 8-50 nucleobases that specifically hybridizes with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA (PLA2 IIA) and inhibits expression of human PLA2 IIA in vitro and in vivo.

The genus comprising the claimed 8-50 nucleobase compounds reads on a broad array of sequences (e.g. thousands of sequences), and the disclosure fails to provide a representative number of species for such a broad genus that provides for the function claimed, *i.e.* that inhibits expression of PLA2 IIA in vitro or in vivo. The specification teaches the human PLA2 IIA expression in vitro comprising the administration of antisense oligonucleotides that are 20 nucleobases in length and share complete homology with the target human PLA2 IIA gene. These teachings are not representative of the genus embracing compounds between 8-50 nucleobases that specifically hybridize with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA (PLA2 IIA) and inhibit expression of human PLA2 IIA in vitro and in vivo.

The disclosure does not clarify the common attributes or provide a representative number of species for adequate description of the encompassed genus of sequences. Concise structural features that would distinguish structures within the claimed genus of sequences from those outside of the genus are missing from the disclosure. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus claimed. Thus, Applicant was not in possession of the claimed genus.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of human phospholipase A2, group IIA comprising the administration of antisense oligonucleotides sharing complete

homology with the target sequence, does not reasonably provide enablement for compositions and methods for the inhibition of phospholipase A2, group IIA in an organism comprising the administration of antisense. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with this claim.

The claim is drawn to methods of inhibiting the expression of phospholipase A2, group IIA in vitro or in vivo comprising the administration of antisense oligonucleotides which specifically hybridize with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The following references are cited herein to illustrate the state of the art of treatment in organisms that involves the delivery of nucleic acid molecules to appropriate cells in an organism. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of in vivo inhibition of target genes. (A. Branch, Trends in

Biochem. Sci. 23: 45-50, *see* entire text for Branch; S. Crooke, Antisense Research & Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using nucleic acid based approaches Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (A. Peracchi et al, Rev. Med. Virol.,14: 47-64, especially at 51).

Agrawal et al also speak to the unpredictable nature of the nucleic acid based therapy field thus: "It is therefore appropriate to study each ... oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80). Cellular uptake of oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense." Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of ... oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; *see* Chirila et al., Biomaterials, 23: 321-342 in its entirety,

especially at 326-327 for a general review of the important and inordinately difficult challenges of the delivery of therapeutic oligonucleotides to target cells).

See Opalinska (Nature Reviews, Vol. 1, pages 503-514, 2002) for a review of the unpredictabilities associated with the in vivo efficacy of double stranded oligonucleotides for target gene inhibition: "Although conceptually elegant, the prospect of using nucleic acid molecules for treating human malignancies and other diseases remain tantalizing, but uncertain." (3rd full paragraph on p. 503). "...it is widely appreciated that the ability of nucleic acid molecules to modify gene expression in vivo is quite variable, ant therefore wanting in terms of reliability." (1st full paragraph on p. 511).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting phospholipase A2, group IIA in vivo comprising the administration of antisense. The specification teaches the inhibition of human synovial phospholipase A2, group IIA encoded by SEQ ID NO: 3 in vitro comprising the administration of antisense oligonucleotides 20 nucleobases in length that share complete homology with the target gene sequence. The specification fails to teach the inhibition of phospholipase A2, group IIA expression in any organism comprising the administration of any antisense which specifically hybridize with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA.

One skilled in the art would not accept on its face the examples given in the specification of the in vitro targeting and inhibition of human synovial phospholipase A2, group IIA using antisense 20 nucleobases in length and sharing complete homology with the target nucleic acid sequence as being correlative or representative of the successful inhibition of phospholipase A2, group IIA expression in an organism comprising the administration of antisense encompassing the broad genus comprising any compound of at least 8 nucleobases that specifically hybridizes with nubleobases 994-1070 of SEQ ID NO. 17, in view of the lack of guidance in the specification and known unpredictability associated with predetermining the efficacy of antisense in inhibiting the target molecule in an organism. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery, and inhibition of target molecule expression in an organism by antisense administered, and specifically regarding the genus of 8 nucleobase compounds claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claim is very broad. The claim is drawn to methods of inhibiting the expression of phospholipase A2, group IIA in vitro or in vivo comprising the administration of antisense oligonucleotides which specifically hybridize with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target molecule

phospholipase A2, group IIA in vivo whereby the its expression is inhibited in vivo. Since the specification fails to provide any particular guidance for the inhibition of phospholipase A2, group IIA expression in an organism comprising the administration of the genus of compounds claimed, and since determination of the factors required for in vivo success is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 12, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al.

Bennett et al (USPN 5,530,114) teach a composition comprising a pharmaceutically acceptable diluent and an antisense oligonucleotide between 8-50 nucleobases in length that specifically hybridizes with at least an 8 nucleobase portion of nucleobases 994-1070 of SEQ ID NO. 17, optionally comprising a phosphorothioate internucleotide linkage and which antisense inhibits the expression of human PLA2 IIA in vitro (see SEQ ID NO. 13 of Bennett et al and accompanying sequence alignment data, see also the abstract, col. 21-23, examples 10-12).

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-10 and 12-14 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cowsert et al.

Cowsert et al (USPN 5,981,732) teach compositions comprising an antisense oligonucleotide between 8-50 nucleobases in length that specifically hybridizes with at least an 8 nucleobase portion of nucleobases 994-1070 of SEQ ID NO. 17, optionally comprising phosphorothioate internucleotide linkages, 2'-O-methoxyethyl sugars, 5-methylcytosines, which oligonucleotide is optionally chimeric, and which compositions comprise a pharmaceutically acceptable diluent and a colloidal dispersion system. The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255,

195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. The sequence cited above that shares less than 100% homology with the target gene (see accompanying alignment data illustrating 94% homology) is presumed to have inhibitory function since sequences with less than 100% homology meet the structural requirements of the claimed invention as indicated in the instant specification under the discussion of "specifically hybridizing" (e.g. pages 9-10 of the instant specification). Therefore, absent evidence to the contrary, since the oligonucleotide disclosed by Cowsert et al meets all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of specifically hybridize with at least an 8 nucleobase portion of SEQ ID NO; 17, of human synovial phospholipase A2, group IIA and inhibiting its expression in vitro. Therefore, absent evidence to the contrary, claims 1, 2, 4-10 and 12-14 are anticipated

by or, in the alternative, obvious over Cowsert et al (See SEQ ID No. 40 of Cowsert, see also the attached sequence alignment data, see also col. 5-8, 16-19, claims 5-9 and 16-20).

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
5-3-06

TC 1600

JANE ZARA, PH.D.
PRIMARY EXAMINER